AD-A278 243

TATION PAGE

DATE	3 REPORT TYPE AND DATES COVERED
	ANNUAL 01 Sep 92 TO 31 Aug 93

4. TITLE AND SUBTITLE

(FY91 AASERT), CELLULAR ANALYSIS OF THE STARTLE REFLEX

5. FUNDING NUMBERS

F49620-92-J-0300
61103D
3484
S4

(2)

6. AUTHOR(S)

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DTIC
ELECTE
APR 20 1994
S F D

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

AFOSR-TR- 94 0224

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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BOLLING AFB DC 20332-0001

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10. SPONSORING/MONITORING AGENCY REPORT NUMBER

2pg

94-11920

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

12b. DISTRIBUTION CODE

Approved for public release;
distribution unlimited

13. ABSTRACT (Maximum 200 words)

In the ASSERT Award we are interested in how dopamine agonists affect baseline startle amplitude as well as the phenomenone of pre-pulse inhibition. To test this, we have been recording the compound action potential generated by an auditory stimulus at the level of the cochlear nucleus in freely moving rats using a bundle of four previously implanted 25 um nichrome wires. Each of the dopamine agonists increased the amplitude of the auditory nerve response (N1 component, latency =0.75 msec - Meloni & Davis, 1993). This effect is larger following repeated administration of d-amphetamine on each of 7 days, indicating that is shows sensitization. This suggests that dopamine agonists ultimately can alter processes at the very beginning of the auditory system, which we believe may have considerable relevance for dopamine-induced disruption of auditory prepulse inhibition as well as auditory distractibility and even auditory hallucinations in people.

DTIC QUALITY INSPECTED 3

94 4 19 040

14. SUBJECT TERMS

15. NUMBER OF PAGES

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRAC
(U)	(U)	(U)	(U)

NSN 7540-01-280-5500

Interim Technical Report
Number: F49620-92-J-0300 (the Assert Award)
Title: Cellular Analysis of the Startle Reflex
PI: Michael Davis

Effects of dopamine agonists on compound action potentials recorded in the cochlear nucleus.

In the Assert Award we are interested in how dopamine agonists affect baseline startle amplitude as well as the phenomenon of pre-pulse inhibition, described earlier. Prior work in our laboratory had found that dopamine agonists such as apomorphine, d-amphetamine or cocaine all increased acoustic startle amplitude (Davis & Aghajanian, 1976; Davis et al., 1975; Davis, 1985). By eliciting startle electrically we deduced that each of these drugs increased startle by acting very early in the acoustic startle pathway (i.e., at or before the cochlear nucleus - Davis et al., 1986; Harty & Davis, 1985).

To test this, we have been recording the compound action potential generated by an auditory stimulus at the level of the cochlear nucleus in freely moving rats using a bundle of four previously implanted 25 μm nichrome wires. Each of the dopamine agonists increased the amplitude of the auditory nerve response (N1 component, latency = 0.75 msec - Meloni & Davis, 1993). This effect is larger following repeated administration of d-amphetamine on each of 7 days, indicating that it shows sensitization. This suggests that dopamine agonists ultimately can alter processes at the very beginning of the auditory system, which we believe may have considerable relevance for dopamine-induced disruption of auditory prepulse inhibition as well as auditory distractibility and even auditory hallucinations in people.

There are only a limited number of ways in which a dopamine agonist could affect the compound action potential. One peripheral mechanism would be via a change in blood pressure at the cochlea. However, other drugs which either increase or decrease blood pressure have not produced consistent effects on the compound action potential (Meloni and Davis, unpublished). Other peripheral mechanisms would be via direct actions on dopamine receptors in the cochlea, which is known to contain dopamine (Eybalin et al., 1993; Gil-Loyzaga & Pares-Herbute, 1989) or the middle ear muscle reflex. Direct actions in the cochlear seem unlikely because we have found that lesions of the substantia innominata in the forebrain block both the excitatory effects of apomorphine on acoustic startle and the facilitation of the compound action potential (Meloni & Davis, 1993), suggesting a central rather than peripheral site where the effects of apomorphine are initiated. A central mechanism would be via the olivary cochlear bundle, through which cells in the lateral superior olive and ventral nucleus of the trapezoid (in rats) project directly to inner and outer hair cells and modulate their activity (cf. White and Warr, 1983). This is an especially intriguing possibility because an efferent brain system which projects directly to the primary auditory receptors has long been suspected to be involved in processes such as sensory gating and attention (Hernandez-Peon, 1956; Oatman, 1971). In fact, we find that local anesthetics applied to the olivary cochlear bundle markedly increase the compound action potential in waking but not anesthetized rats (Meloni and Davis, unpublished). If dopamine agonists somehow inhibited olivary cochlear function, this might lead to an increase in baseline startle amplitude and/or to a disruption of prepulse inhibition. In fact, this inhibitory system is especially effective in altering responsivity to relatively weak stimuli (cf. Wiederhold, 1986) and has been shown to be critical for modulating auditory signals in the presence of masking noise (Nider & Nider, 1970; Kawase & Liberman, 1993). In rats, disruption of prepulse inhibition by apomorphine generally has been most effective when the intensity separation between the prepulse and background noise has been smaller than about 10 dB (Davis et al., 1990). Hence, another major goal of the proposed studies will be to evaluate the role of the olivary cochlear bundle in prepulse inhibition and its disruption by apomorphine.